"THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"

Dissertation submitted for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH – I

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY, CHENNAI.

March 2008.

CERTIFICATE

Certified that this dissertation entitled "**THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"** is a bonafide work done by **Dr.PL.ALAGAMMAI, M.D.,** Post Graduate student in Internal Medicine, Institute of Internal Medicine, Madras Medical College, Chennai- 600003, during the academic years 2005 -2007.

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DECLARATION

I solemnly declare that the dissertation entitled "**THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS"** is done by me at Madras Medical College, Government General Hospital, Chennai during 2005 -2007 under the guidance and supervision of **Prof.D.RAJASEKARAN,M.D.** This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of the requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE (BRANCH I)**.

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CONTENTS

INTRODUCTION

Type 1 Diabetes is a common autoimmune endocrine disease in children and adolescents. It is a clinical syndrome in which the destruction of the pancreatic islet β-cells leads to progressive insulin deficiency and hyperglycemia, which in turn gives rise to micro vascular complications such as retinopathy, nephropathy, and neuropathy as well as macro vascular complications.[42]

The presence of auto antibodies targeted against β-cell antigens represents the autoimmune character of Type 1 Diabetes (T1D). Due to this autoimmune basis, individuals with T1D are at increased risk for the development of additional autoimmune disorders compared with the general population[1]. Commonly coexisting immune-mediated disorders are Autoimmune Thyroid Disease (AITD), Coeliac Disease (CD), Addison's Disease (AD) and pernicious anaemia.[1,2,42,18] These diseases are associated with organ-specific autoantibodies: Thyroid peroxidase (TPO) thyroglobulin (TG), TSH receptor autoantibodies with AITD, endomysial autoantibodies and transglutaminase autoantibodies with CD, and 21-hydroxylase

autoantibodies with AD. Using these autoantibodies, organ-specific autoimmunity may be detected before the development of autoimmune clinical disease.[2]

The most prevalent among these is thyroid autoimmunity.[11,2,28,19] Its prevalence varies from 8 to 50% depending on the age, sex, and ethnic origin of the subjects. In the general population, thyroid autoimmunity is more frequent in female subjects and prevalence increases with age. In diabetic patients, age and sex distributions are similar, but the prevalence is higher and increases with duration of the disease.[4]

Most patients with thyroid autoimmunity are asymptomatic[25] . Even if symptomatic; symptoms may be attributed to diabetes. So, the diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult[7]. Though not clinically evident, underlying hypothyroidism has its own impact on morbidity particularly by exacerbating the coexisting dyslipidemia commonly found in type 1 diabetes and thus increases the risk of cardiovascular diseases.

Because of this high prevalence, lack of clinical features and the impact on morbidity, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease.

AIMS AND OBJECTIVES

- To study the prevalence and pattern of thyroid disorders in Type 1 Diabetic patients.

- To find out thyroid autoimmune status among them.

- To correlate thyroid autoimmunity with thyroid dysfunction.

- To assess any age/gender/diabetes duration difference.

REVIEW OF LITERATURE

Background and History:

Type 1 diabetes results from a cellular mediated autoimmune destruction of the β-cells of the pancreas, leading to absolute insulin deficiency. It is frequently associated with other autoimmune diseases and autoantibodies[1]. The most prevalent autoimmune disease in type 1 diabetes is Hashimoto's thyroiditis.[41]The increased incidence of thyroid autoimmunity in type 1 diabetes was first reported in 1963[20].Since then many series have been reported. Thyroid autoimmunity is generally less prevalent in blacks than whites for unknown reasons[15]. The exact prevalence of AITD among Indian adolescents with type 1 diabetes is still unknown.

Autoimmunity:

Autoimmunity represents the end result of the breakdown of one or more of the basic mechanisms regulating immune tolerance. The essential feature of an autoimmune disease is that tissue injury is caused by the immunologic reaction of the organism with its own tissues. Autoimmunity can be organ specific or non organ specific. The two most common organ specific autoimmune diseases are AITD (autoimmune thyroid diseases) and T1D (type 1 diabetes). Organ-specific autoimmune diseases can be part of autoimmune polyglandular syndromes (APS).

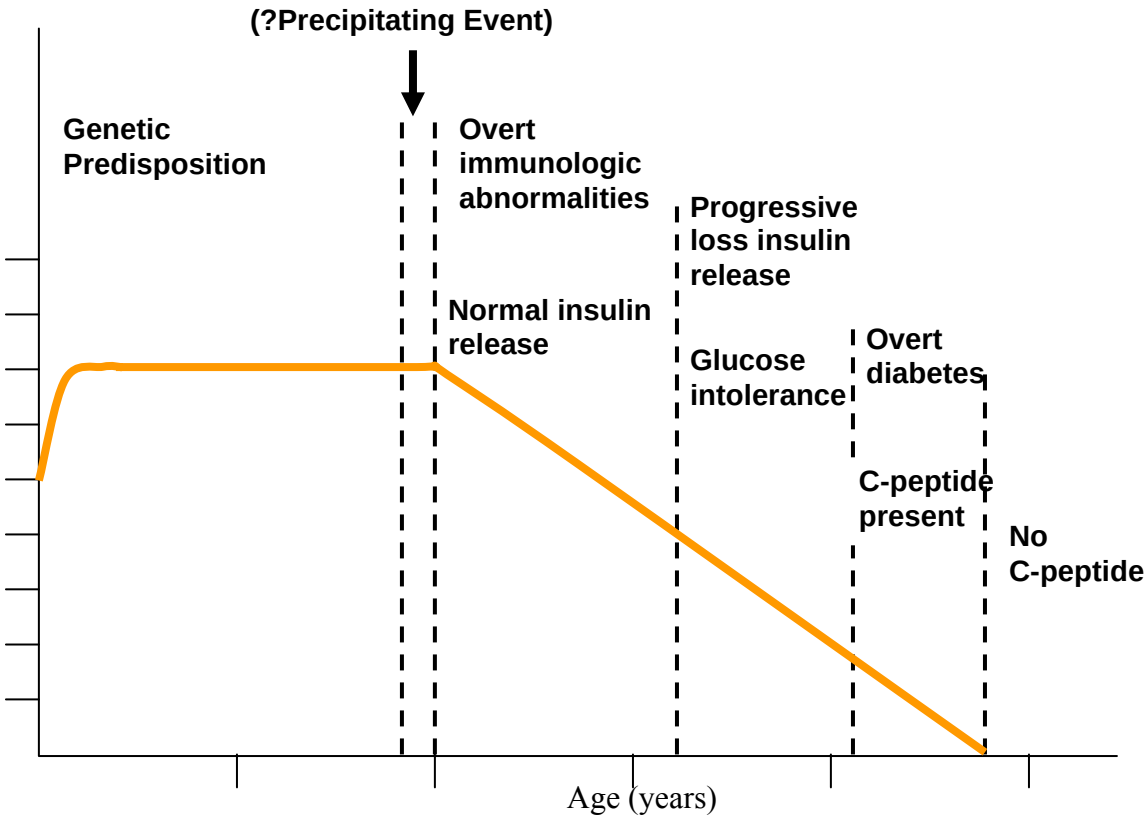
Type 1 Diabetes (T1D):

The model of T1D is a chronic autoimmune disease beginning with genetic susceptibility and progressing to autoimmunity leading to destruction of β-cells. Insulin autoantibodies are often the first expressed autoantibody. Other antibodies are against islet cell, GAD65, and IA-2. These autoantibodies may be present for years before the diagnosis of diabetes. Abnormalities of iv and oral glucose tolerance testing precede the diagnosis of overt diabetes and this may persist for years; ultimately leading to overt diabetes.[2]

Type 1A diabetes(90%) is autoantibody positive ,type 1 B diabetes(10%) is autoantibody negative. Type 1 diabetes can present at any age , peak age of presentation being puberty. Clinical presentation is with features of hyperglycemia, sometimes directly as diabetic ketoacidosis. Patients are insulin dependant from the beginning. They develop diabetes related macrovascular and microvascular complications.

Type 1 diabetes is commonly associated with other autoimmune diseases like AITD, celiac disease and addison's disease. It can also be seen in autoimmune polyendocrine syndromes 1/ 2. [22]

Stages in development of Type 1 Diabetes[40]



Autoimmune thyroid disease(AITD):

The term "autoimmune thyroid disease" is used to describe all autoimmune thyroid conditions, including Graves' disease, Hashimoto's thyroiditis, and various other disorders (eg, postpartum thyroiditis, most cases of silent thyroiditis). The most common presentation is the presence of positive antithyroid antibodies in a euthyroid patient.[8] The antithyroid antibodies can be anti thyroid peroxidase (anti TPO) antibodies or

antithyroglobulin antibodies or anti TSH receptor antibodies.[3] Anti TPO antibodies and anti Tg antibodies are prevalent in approximately 13% and 11% of general population respectively but the prevalence is much less in blacks; TPOA positivity seen in only 5% of population. [2,15]

Hypothyroidism with or without goiter is more common than hyperthyroidism. Hypothyroidism is prevalent in about 4.5 - 5% of the population (0.5% clinical and 4.5% subclinical) and hyperthyroidism in about 1.3% (0.5% clinical and 0.7% subclinical).[15]Autoimmune thyroiditis, specifically Hashimoto's thyroiditis, is more prevalent in persons with various autoimmune and nonautoimmune disorders like congenital rubella syndrome and some genetic conditions like Down's syndrome. It can be a part of autoimmune polyendocrine syndromes type 1-3.[22]

Genetic basis:

The major histocompatibility complex (MHC) has been extensively studied in autoimmune diseases. The highest-risk human leukocyte antigen (HLA) genotype for T1D is DR3-DQ2, DR4-DQ8. Subjects expressing this genotype have a 5% risk for T1D by 15 yrs of age.

Cross-sectional analysis in subjects with T1D has shown an association with the genotype DR3-DQ2, DR4-DQ8 and the haplotype DR3-DQ2. [2]

Screening blood donors for TPO autoantibodies has shown an association with DR3 and DR5.[10]

In families with multiple members affected with T1D and AITD, DR3-DQ2 has been linked with AITD and T1D.[34]HLA DQB1*0401 can be a predisposing genetic marker for the development of AITD in patients with T1D[21]. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a non-HLA susceptibility gene for type 1 diabetes on chromosome 2q33 expressed on activated CD4+ and CD8+ T-cell membranes. Polymorphisms within the CTLA-4 gene have been linked to AITD. Polymorphism of PTPN22 gene expressed in T cells has been associated with T1D and Graves disease. The MHC I-related gene A (MIC-A) has been associated with T1D[2]

Selected genes associated with T1D and related autoimmune diseases[2]

Gene	Associated diseases
HLA	
DR3-DQ2, DR4-DQ8	T1D
DR3; DR5	AITD
DR3-DQ2	CD
DR3-DQ2, DR4-DQ8	AD
MIC-A	T1D,CD.AD
PTPN22	T1D.AITD,AD
CTLA-4	T1D, AIT

Autoimmune polyendocrine syndromes(APS)[39,22]

These are APS types I, II, III and IPEX.

APS type I:

It is an autosomal recessive condition with mutations in an autoimmune-suppressor gene (*AIRE*, for autoimmune regulator), which encodes a transcription factor. Affected persons will have any two of the following conditions — mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease. Mutations in the *AIRE* gene cause many other autoimmune diseases, and affected patients are at risk for the development of multiple additional autoimmune diseases over time, including type 1A

diabetes(18%), hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, ovarian atrophy, and keratitis.

APS II:

It is also called Schmidt's syndrome characterized by Addison's disease plus hypothyroidism.20% of individuals can develop type 1 diabetes. The syndrome is associated with HLA DR3/DR4.

APS III:

Autoimmune polyendocrine syndrome type III refers to thyroid autoimmunity plus another autoimmunity (but not Addison's disease)

IPEX**:** (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked)

Extremely rare disorder with X linked inheritance characterized by fulminant, widespread autoimmunity and type 1A diabetes.

Effect of Diabetes on Thyroid function:

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process.[18]

In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status. Poorly controlled diabetes, both Type 1 and Type 2, may induce a "Low T3 state"[16] characterized by low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations.Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5' monodeiodination reaction. Studies indicate that it may be the long term diabetic control that determines the plasma T3 levels . Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak. TSH responses and "low T3 state" may normalize with improvement in glycemic status but even with good diabetes control, the normal nocturnal TSH peak may not be restored in

C-peptide negative patients i.e. those with totally absent pancreatic beta cell function.[18]

Diabetes mellitus influences the assessment of thyrotoxicosis by falsely decreasing the blood levels of thyroxine (T4) and triiodothyronine (T3) during severely uncontrolled hyperglycemia. [26]

Metabolic effects of Thyroid dysfunction on Diabetes:

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements[17]. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, increased insulin degradation, and probably increased insulin resistance. Indeed, thyrotoxicosis may unmask latent diabetes.[26]In practice, there are several implications for patients with both diabetes and hyperthyroidism. First, in hyperthyroid patients, the diagnosis of glucose intolerance needs to be considered cautiously, since the hyperglycemia may improve with treatment of thyrotoxicosis. Second, underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia. Third, in

diabetic patients with hyperthyroidism, physicians need to anticipate possible deterioration in glycemic control and adjust treatment accordingly. Restoration of euthyroidism will lower blood glucose level.

Although wide-ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestation of these abnormalities is seldom conspicuous.[25]The synthesis and release of insulin is decreased but there is reduced rate of insulin degradation that may lower the exogenous insulin requirement. The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis. The net effect is an increased risk of recurrent hypoglycemia in a diabetic individual. [18,13]

More importantly, hypothyroidism is accompanied by a variety of abnormalities in plasma lipid metabolism, including elevated triglyceride and low-density lipoprotein (LDL) cholesterol concentrations. Even subclinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in diabetes and further increase the risk of cardiovascular diseases.[7,32]

Diabetes and Thyroid diseases – Interactions:

Clinical Condition	Effect on Glycemia	Effect onThyroid function
Diabetes mellitus - In euthyroid individuals	--	↓ Serum T3 ↑ rT3 ; ↓ TSH response to TRH; impaired nocturnal TSH peak.
Hyperthyroidism - In euglycemic individuals	Glucose intolerance - in 50% cases Overt diabetes in 2-3%	
Hyperthyroidism- In diabetic individuals	Deterioration of - diabetes control	High incidence of optic neuropathy
Hypothyroidism- In diabetic individuals	Predisposition to - recurrent hypoglycemia. Exacerbation of dyslipidemia.	

Thyroid disorders in Type 1 Diabetes:

Prevalence pattern:

The prevalence of thyroid autoimmunity and thus thyroid dysfunction is high in T1D. 15 to 30% of subjects with type 1 diabetes (T1D) have autoimmune thyroid disease. [2,3,9,12]

As in general population autoimmune thyroid diseases are common in females and prevalence increases with age.[10,15,19,23] Additionally, prevalence increases with increasing duration of Diabetes. [4,9,23]

Thyroid autoimmunity is considered to be present if the patient is positive for Thyroid peroxidase (TPO) or thyroglobulin (TG) or TSH receptor autoantibodies. Among these thyroid peroxidase antibody (TPOA) is a very sensitive marker.[11] TgAb alone in the absence of TPOA is not significantly associated with thyroid disease.[15] The presence of GAD antibodies in T1D was associated with an almost two-fold greater risk of thyroid autoimmunity than in the absence of GAD seroreactivity.[20,33,34] There is an increased frequency of thyroid dysfunction in siblings of

diabetic patients also.[41,14] One-third of women with type 1 diabetes will develop post partum thyroiditis. [37]

Thyroid autoimmunity manifests commonly as hypothyroidism. But,hypothyroidism has a lower prevalence than thyroid autoimmunity according to most studies. This is because, it may take years for patients with positive autoimmune serology to develop thyroid disease.[12] With follow-up of almost 20 yrs, the development of hypothyroidism in the population with T1D and TPO autoantibodies approached 80% in life table analysis.[2] Patients who were TPO positive were almost 18 times as likely to develop hypothyroidism as patients who were TPO negative.[6,12,25]

Hyperthyroidism is much less commonly reported, with a prevalence similar to general population rates of 1% .

Clinical aspects:

T1D patients with AITD may belong to a subgroup of diabetic patients with severe form of diabetes which is characterized by a higher prevalence of ketoacidosis.[28]

Most of the diabetic patients are asymptomatic at diagnosis of hypothyroidism[25] ie. most of them have only subclinical hypothyroidism. Even if symptomatic; symptoms can easily be misinterpreted to be due to underlying diabetes because people with this condition may experience fatigue, weight gain, feeling cold, dry skin and hair, constipation and slowed thinking. T1D can also produce menstrual disturbances by itself, thus misleading. [27] Edema, fatigue, pallor, and weight gain can be attributed to be due to diabetic nephropathy.[7]

Symptoms of hyperthyroidism in people with type 1 diabetes can produce symptoms like weight loss despite increased appetite and fatigue and may be attributed to poor glycaemic control.

So, both hypo and hyperthyroidism can go unnoticed clinically necessitating other methods for diagnosis. Apart from controlling morbidity related to thyroid dysfunction, early diagnosis is particularly essential to prevent the adverse impact of these disorders in diabetic individuals. Screening for thyroid dysfunction may prevent the development of overt thyroid dysfunction and may allow early treatment of hyperlipidemia,prevention of associated cardiovascular complications , and metabolic bone disorders.

Thyroid peroxidase antibodies is more sensitive than other antibodies in identifying thyroid autoimmunity.[15,11] So screening for TPOA helps in finding out those with AITD. Thyroid ultrsonogram abnormality was a sensitive but non-specific marker of AITD and is therefore unsuitable for screening purposes.[30]

The availability of the highly sensitive immunoassay for serum TSH (with detection limit of <0.1 mU/l) provides a major advance in the diagnosis of thyroid disorders. It is the most reliable and sensitive screening test for thyroid dysfunction and allows both hypothyroidism and hyperthyroidism to be diagnosed with certainty. In addition, subclinical

thyroid dysfunction can only be diagnosed by an abnormal TSH because the serum T3 and T4 are normal and, by definition, the patients are usually asymptomatic.[7]

The American Diabetes Association and several authors.[7,14,16,17,18,23] recommend annual screening for thyroid disease in all type 1 diabetes subjects. TSH measurement is considered the most sensitive way to identify patients with thyroid dysfunction, as autoantibodies may persist for many years without thyroid dysfunction.[4] However, the presence of thyroid autoantibodies increases the risk for thyroid disease and so particularly those with positive TPO antibodies should undergo screening. Despite the association between positive thyroid TPO antibodies and the subsequent development of hypothyroidism, annual measurement of serum TSH constitutes the preferred screening test to detect asymptomatic thyroid dysfunction.[25]

MATERIALS AND METHODS

Study design:

Cross sectional observational study to analyse the prevalence of thyroid disorders and thyroid autoimmunity among Type 1 Diabetes.

Setting:

Institute of Internal Medicine and Department of

Diabetology ,

Government General Hospital**,**

Madras Medical College,

Chennai**.**

Approval:

The study was approved by the ethical committee of Government General Hospital, Madras Medical College.

Study population:

Patients were enrolled from the patient population who attended the out patient clinic of Department of Diabetology and Institute of Internal Medicine between Nov. 2005 to Feb 2007. 64 patients among them satisfied criteria for inclusion into the study. Patient list did not include paediatric group since they were not attending our hospital.

No. of patients enrolled : 71

No. of patients included : 64

No. of patients excluded : 7

Inclusion criteria:

Established cases of Type 1 Diabetes , diagnosed based on standard criteria [Symptoms of diabetes and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l) or FPG ≥126 mg/dl (7.0 mmol/l) or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l)] and insulin dependance proved by C peptide level of < 1 ng/ml.

Exclusion criteria:

- Pregnancy
- Evidence of other autoimmune diseases like Addisons disease, vitiligo, autoimmune hepatitis, rheumatoid arthritis,SLE.
- Multinodular goiter, known thyroid disease with negative thyroid autoimmunity.
- Past history of thyroid surgery or radioiodine therapy.

`Consent:

Patients were informed about the details of the test performed and blood sample collected with consent.

Sample collection:

Venous blood sample collected in 8 hrs fasting state. After serum separation, sample was sent for analysis.

Method of testing:

T3,T4, TSH	--	Radio Immuno Assay.
Thyroid peroxidase Antibodies	--	Enzyme Linked Immuno Sorbent Assay.

Normal ranges:

T**3**	0.8 – 1.4	ng/ml
T4	4.2 – 11	µg/dl
TSH	0.5 – 5	mIU/ ml
TPOA	upto 40	IU/ml

Result interpretations:

`

- Any T3 /T4 value above the upper limit of normal along with a low TSH < 0.5 mIU/ml is considered as hyperthyroidism.
- Any T3 /T4 value below the lower limit of normal along with an elevated TSH > 5mIU/ml is considered as hypothyroidism.
- TSH > 5mIU/ml along with normal range T3 , T4 is considered as subclinical hypothyroidism.
- TSH < 0.5 mIU/ml along with normal range T3 , T4 is considered as subclinical hyperthyroidism.
- Thyroid autoimmunity is considered to exist if TPOA level is > 40 IU/ml and not to exist if it is lesser.

Statistical analysis:

Statistical analysis was done using standard formulae SPSS (Statistical Package for Social Sciences) in windows Dos version.

Base line data like age, gender, duration of diabetes were collected. Patients were categorized based on their thyroid status and thyroid autoimmune status.

The significance of difference between means in two groups was calculated using student t test and the significance of difference in proportions using chi-square test. Fisher exact test was used when any one of the values was less than 5 in chi-square test. 2 x 2 tables were constructed for each variable and chi square value for a degree of freedom calculated. Statistical significance at 5% levels was taken for p value < 0.05 and at 1% levels $p < 0.001$.

OBSERVATIONS AND RESULTS

TOTAL NUMBER OF PATIENTS (n) : 64

FEMALE : 33

MALE : 31

AGE : 13-32 YEARS

(MEAN - 20.2 $\pm$ 5.16)

TOTAL NO. OF HYPOTHYROID PATIENTS : 8 (12.5%)

MALE : 2

FEMALE : 6

SUBCLINICAL HYPOTHYROIDISM : 7

OVERT HYPOTHYROIDISM : 1

TOTAL NO. OF HYPERTHYROID PATIENTS. : NIL

TOTAL NO. OF PATIENTS POSITIVE FOR TPOA

ie. PATIENTS WITH AITD. : 12 (18.75%)

MALE : 4

FEMALE : 8

TOTAL NO. OF TPOA PATIENTS WITH

HYPOTHYROIDISM : 7 out of 12

(58%)

TOTAL NO. OF HYPOTHYROID PATIENTS WITH

TPOA : 7 out of 8

(87.5%)

MEAN AGE OF PATIENTS WITH AITD : 21.2 $\pm$ 5.6 YRS

MEAN DURATION OF DIABETES OF PATIENTS

WITH AITD : 4.5 $\pm$ 3.5 YRS

TABLE 1 : THYROID STATUS IN RELATION TO GENDER.

THYROID STATUS	TOTAL NO. (IN%)	GENDER	
		MALE	FEMALE
EUTHYROID	56 (87.5%)	29 (45.3%)	27 (42.2%)
HYPOTHYROID	8 (12.5%)	2 (3.1%)	6 (9.4%)
HYPERTHYROID	nil		

On comparing the female : male 3:1 ratio by **chi square test** , the p value is 0.1573 which is > 0.05 . So, the association between gender and hypothyroidism is not significant indicating that there is no significant gender difference among hypothyroid and euthyroid type 1 diabetics as per this study.

CHART 1: THYROID STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS.

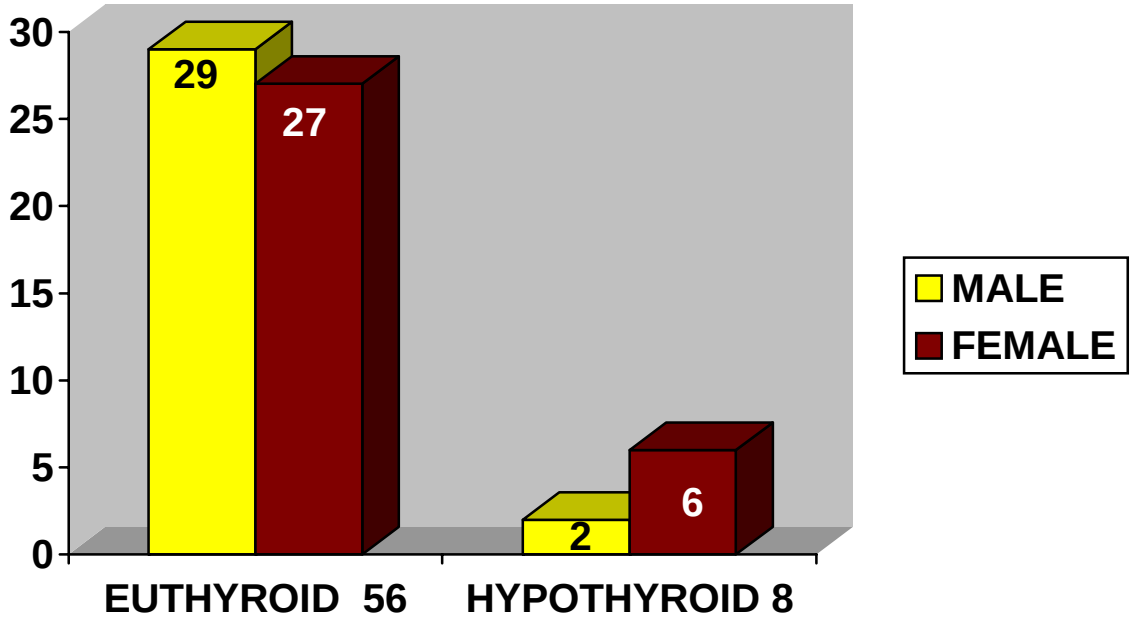
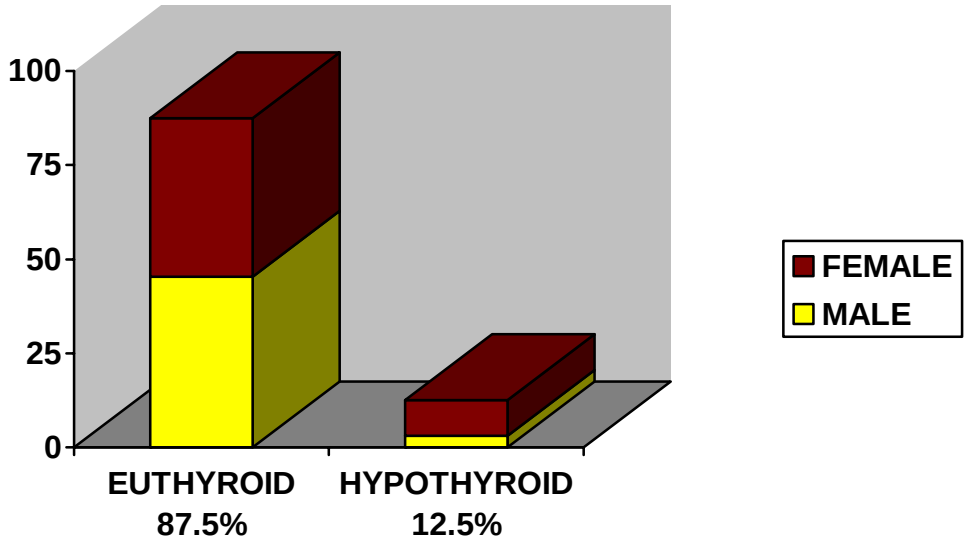


CHART 2 : THYROID STATUS IN RELATION TO GENDER IN PERCENTAGE.



Euthyroid- Male - 45.3% Female - 42.2%
Hypothyroid - Male 3.1% Female - 9.4%

TABLE 2: THYROID AUTOIMMUNITY STATUS IN RELATION TO GENDER.

THYROID AUTOIMMUNITY	TOTAL (IN %)	GENDER	
		MALE	FEMALE
TPOA NEGATIVE	52 (81.25%)	27 (42.25%)	25 (39%)
TPOA POSITIVE	12 (18.75%)	4 (6.25%)	8 (12.5%)

On comparing the female : male ratio 2:1 by **chi square test ,** the p value is 0.2482 which is > 0.05 . So, the association between gender and thyroid autoimmunity is not significant indicating that there is no significant gender difference among those who are positive for TPOA and those who are negative for the same in type 1 diabetics as per this study.

CHART 3: THYROID AUTOIMMUNE STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS.

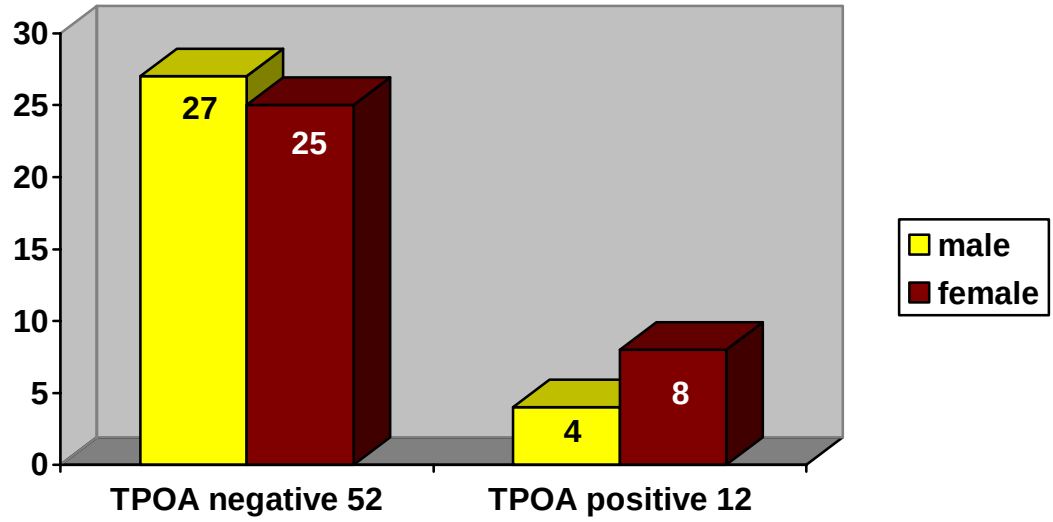
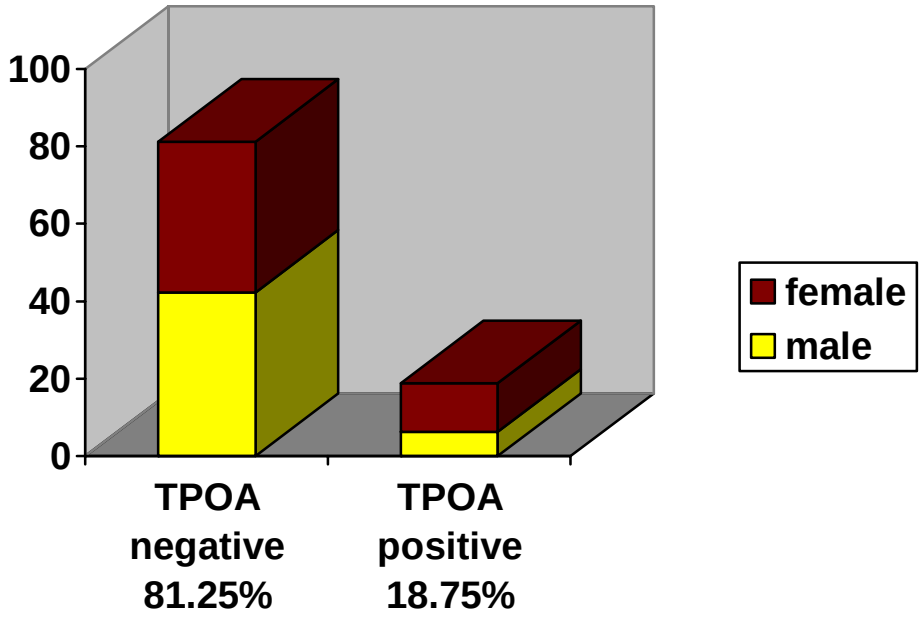


CHART 4: THYROID AUTOIMMUNE STATUS IN RELATION TO GENDER IN PERCENTAGE.



TPOA negative , Male -42.25% Female - 39%
TPOA positive, Male - 6.25% Female - 12.5%

TABLE 3 : CORRELATION BETWEEEN THYROID FUNCTION AND AUTOIMMUNITY.

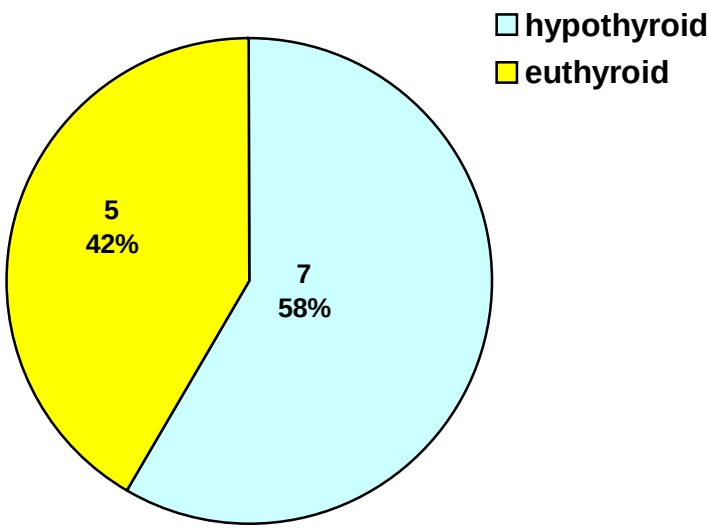
CATEGORY	HYPOTHYROID	EUTHYROID	TOTAL
TPOA POSITIVE	7 (58%)	5 (42%)	12
TPOA NEGATIVE	1 (2%)	51 (98%)	52
TOTAL	8	56	64

Values in brackets represent row percentage.

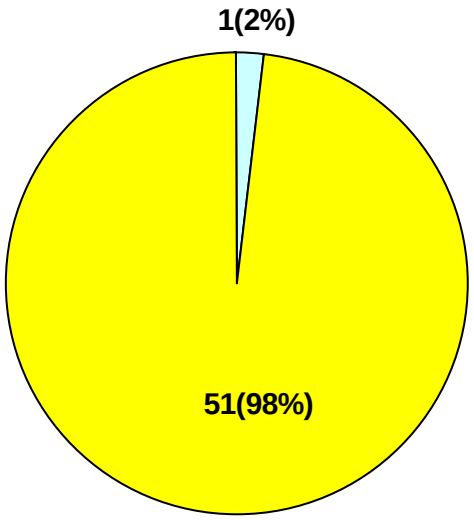
58% of TPOA positive patients are hypothyroid whereas only 2% of TPOA negative patients are hypothyroid. 87.5% of hypothyroid patients are TPOA positive whereas 12.5% of them are TPOA negative. On comparing these two values by **chi square test ,** the p value is 0.001 which is statistically significant at 1% levels. So, the association between thyroid autoimmunity and hypothyroidism is significant indicating that hypothyroidism is more prevalent among TPOA positive individuals than in TPOA negative individuals.

CHART 5: CORRELATION BETWEEN THYROID FUNCTION AND THYROID AUTOIMMUNITY.

TPOA positive



TPOA negative



On assessing TPOA status as a predictor for development of thyroid dysfunction , the positive predictive value is 58% and the negative predictive value is 98%

TABLE 4: THYROID AUTOIMMUNITY IN RELATION TO DURATION OF DIABETES.

AUTOIMMUNE STATUS	MEAN DURATION OF DIABETES IN YEARS $\pm$ SD
TPOA POSITIVE	4.5 ± 3.5
TPOA NEGATIVE	3.2 ± 1.9

On comparing the the two means by **student t test** , the p value is 0.081 whish is < 0.05. So, the association between thyroid autoimmunity and duration of diabetes is not significant indicating that prevalence of AITD is not related to duration of diabetes as per this study.

TABLE 5: THYROID AUTOIMMUNITY IN RELATION TO AGE OF THE PATIENTS.

THYROID AUTOIMMUNITY	MEAN AGE IN YEARS $\pm$ SD
TPOA POSITIVE	21.2 ± 5.6
TPOA NEGATIVE	20 ± 5

On comparing the two means by **student t test,** the p value is 0.478 . So, the association between prevalence of thyroid autoimmunity and age of diabetics is not significant, indicating that prevelance of AITD is not related to age of the patients as per this study.

INTERPRETATION OF RESULTS:

- Most of the TPOA positive individuals have abnormal thyroid function. Positive predictive value is 58%.

- Abnormal thyroid function is mainly in the form of subclinical hypothyroidism.

- Hypothyroidism is more common among those who are positive for TPOA; however hypothyroidism is seen in TPOA negative subjects also.

- Though the actual numbers are high, there is no statistically significant difference in age, sex, duration of diabetes between TPOA positive and TPOA negative individuals.

DISCUSSION

Prevalence of Thyroid autoimmunity in Type 1 Diabetes:

We confirmed the high prevalence of a second organ-specific autoimmune manifestation in individuals with type 1 diabetes. By cross – sectional analysis the prevalence of thyroid autoimmunity in our study population is 18.75%. (12 out of 64). This is in concordance with many other similar studies from various parts of the world. Most of the studies state the prevalence to be between 15 to 30%. Roldán MB et al [11] -17.6%; Prázný M[17] - 22%, McCanlies E[43]-26.6% , Maugendre D et al[19] -17%

Initial screening of type 1 diabetic patients at the time of diagnosis, for the presence of thyroid antibodies was done by Gemma et al in march 2007[4] and O Kordonouri et al[23] in 2005 and they found out TPOA positivity in 14.2% and 15.4% respectively.

Study by Aaron Hanukoglu et al[41] is a multicentered cross sectional study which included both newly diagnosed as well as previously diagnosed patients .They give the prevalence as 27%. Same study says the prevalence in first degree relatives as 25%. Similar single time measurement of antibodies was done by Jennifer M. Barker et al[34] which showed the prevalence as 29%. They actually found an association between thyroid autoimmunity and positivity for Anti GAD antibodies & HLA DR3-DQ2 homozygosity. Comparable value of 26% and a similar HLA association was given by Kim EY et al.[21]

Many longitudinal studies have shown a still higher prevalence due to late appearance of thyroid peroxidase antibodies. Adriana Franzese et el[28] diagnosed 50% of AITD patients at initial screening , remaining 50% on follow up. Longitudinal study by Guillermo E. Umpierrez et al[6] has shown it to be 33% but most of tested positive in the beginning itself.

A study by Menon et al[35], conducted in Department of Pediatrics, All India Institute of Medical Sciences, New Delhi in 2001, is the only Indian study available in this context. According to this study TPO

prevalence is 54.3%. This is a higher value when compared to our study as well as many other studies. But the limitation of this study is that, only 35 patients were included.

Sarah J. Glastras et al[12] and D Hansen et al[30] give relatively lower values of 7.8% and 12.9% respectively.

While most of the studies included patients of any age, the one by Miguel Fernandez-castaner et al [38] is similar to ours. They included only adult population of age > 14 years and found out the prevalence to be 27.9%

Thus, our study on type 1 diabetes supports previous studies in terms of AITD prevalence.

Prevalence of Thyroid dysfunction in Type 1 Diabetes:

The reported prevalence of thyroid dysfunction in diabetic populations varies widely between studies. But, thyroid dysfunction is seen particularly in those who are positive for thyroid autoimmunity and so the presence of thyroid autoimmunity is considered to predict the future development of thyroid dysfunction.

O Kordonouri et el[23] performed a long term, large scale study, which included 659 T1D patients . The cumulative incidence of hypothyroidism at 10 years of observation time was 0.69 (0.08) in positive anti- TPO compared with 0.12 (0.05) in 539 patients with negative anti-TPO measurements ($p < 0.001$)

Guillermo E. Umpierrez et al[6] showed a prevalence of thyroid dysfunction to be 33%. All patients had hypothyroidism mostly subclinical. None had hyperthyroidism. 80% of them were positive for TPOA antibodies. Among the TPOA positive individuals, 83% of females and 51% of males developed hypothyroidism on follow up. In their study, TPOA

positivity as a predictor for development of thyroid dysfunction was assessed and they found out 67% positive predictive value and a 90% negative predictive value. As per their study, patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54).

Comparison with study by Guillermo E. Umpierrez et al:

	GUILLERMO E. UMPIERREZ [6]	OUR STUDY
n	58(F-32,M-26)	64(F-33,M-31)
Prevalence of thyroid dysfunction	33%	12.5%
TPOA positivity in patients with abnormal thyroid function	80%	87.5%
Positive predictive value of TPOA	67%	58%
Negative predictive value of TPOA	90%	98%

Our study is comparable to this study in all terms except that this study was a longitudinal study, where they did assessment for TPOA every 4 years and thyroid function on yearly basis.

Miguel Fernandez-castaner[38] investigated 111 adult T1D patients and found 15.3% thyroid dysfunction , and all of them were positive for thyroid antibodies . None of the TPOA negative individuals developed thyroid function abnormality. Similarly in the report by Maugendre D et al [19] 24% had abnormal thyroid function among anti-TPO positive patients, while none among those who were negative for the antibody. Gemma C et al is in favour with this.

Actually, as seen in many studies, hypothyroidism occurs in TPOA negative individuals also. This may be due to unknown reasons or due to alternative etiologies. Sarah J. Glastras[12] reported 46% thyroid dysfunction among TPOA positive patients whereas it was 3.6% in negative patients. In our study 2% of TPOA negative patients are hypothyroid. This warrants screening all T1D for thyroid function irrespective of their thyroid autoimmune status.

In the Indian study by Menon PS et al[35] abnormal thyroid function was found in only 1 among 19 TPOA patients .

Similar to the report by Guillermo E. Umpierrez et al [6], all our patients with thyroid dysfunction had only hypothyroidism. Most of them were subclinical.While we didn't find any hyperthyroid patients, hyperthyroidism has been reported as a presentation of thyroid autoimmunity in T1D in several studies. [4,11,28]

In the study by Gemma C[4] et al, 72% of patients with thyroid autoimmunity developed thyroid dysfunction. 68% hypothyroidism, 4% hyperthyroidism. Roldán MB et al[11] found 11% subclinical hypothyroidism, 3% overt hypothyroidism, 3% subclinical hyperthyroidism and 6% overt hyperthyroidism among those who were positive for AITD. Adriana Franzese et al[28] investigated 37 DM1 patients with TPO-AB, the prevalence of hypothyroidism was 16% and that of hyperthyroidism was 4% among them.

On the whole, in agreement with many similar reports, we observed a higher prevalence of thyroid dysfunction mostly as subclinical hypothyroidism in type 1 diabetes than in the general population, especially in patients with positive TPO antibodies.

Thyroid autoimmunity in relation to gender:

Generally thyroid autoimmunity is more common in females than in males, this holds good for T1D also as per many cross-sectional as well as prospective studies. But there are studies which showed equal prevalence in both the gender. In our study, though the actual number of females was high, with a F: M ratio of 2:1, it was not of statistical significance. This may be due to two reasons. 1. Actual prevalence being equal; 2. Smaller study population.

Gemma C et al [4] reported female preponderance. 18.3% females had AITD whereas it was 7% in males. Olga Kordonouri et al[9] showed a similar female preponderance and they had 63% of AITD patients as females.

Reports by Holl RW et al[10] O Kordonouri et al[23] Adriana Franzese et al[28] Jennifer M. Barker et al[34]support this gender difference.

Miguel Fernandez-castaner et al[38] investigated 814 T1D patients and found a female predominance among TPOA positive patients but not among Tg - Ab positive patients.

Guillermo E. Umpierrez et al [6] found a higher incidence of hypothyroidism in TPO positive females than in antibody positive males, but reported the prevalence of thyroid autoimmunity as equal in both the sex.

Menon PS et al[35] showed that sex doesn't influence the development of thyroid autoimmunity among Indian paediatric population.

Sarah J. Glastras et al[12] D Hansen, FN Bennedbaek et al[30] D Hansen Penny R et al[31] Aaron Hanukoglu et al [41] Maugendre D et al[19] are in agreement with equal prevalence in both the sex.

As in general population, thyroid autoimmunity is expected to be more common in females, but it may not be so in all population.

Thyroid autoimmunity in relation to age:

Many studies have shown that the prevalence of thyroid autoimmunity is high among older patients than younger patients. But in our study we didn't find a significant age difference between TPOA positive and TPOA negative individuals. This may be because of the reason that we included only patients of age >12. But there are reports, where presence of TPOA is not influenced by age .

Olga Kordonouri et al[9] states that the prevalence of significant thyroid antibody titers increases with increasing age of patients and reached its maximum in the 15- to 20-year age group. Holl RW et al[10] found the prevalence of AITD to increase dramatically with age. O Kordonouri R, Hartmann et al [23] reports the prevalence to be high in > 12 years age group. Jennifer M. Barker et al[34] Czerniawska E et al [25] agree the higher prevalence in older age.

In the study by Gemma C et al[4] there is a significant age difference between those who develop thyroid dysfunction and those who remain euthyroid among the TPOA positive subjects. Thyroid function abnormality being more common among those who were older at the onset of diabetes. But age of onset does not influence the positivity for the antibodies.

Guillermo E. Umpierrez et al,[6] Sarah J. Glastras et al ,[12] DHansen et al [30] Maugendre D et al [19] observed no significant age difference.

The Indian study by Menon PS et al[35] did not analyse the age difference .

Gregory Goodwin et al [1] is totally against other reports by stating that the risk of thyroid autoimmunity is more in sibling pairs with younger age of onset of diabetes.

The influence of age of onset of diabetes or age of the patient on development of AITD may/may not be there depending on the population.

Thyroid autoimmunity in relation to duration of diabetes:

According to many prospective studies incidence of thyroid autoimmunity increases as years pass by since the diagnosis of diabetes. The net result would be a higher prevalence of AITD among patients with longer duration of diabetes than the newly diagnosed cases. But in our study there is no significant difference in duration of diabetes between, TPOA positive and TPOA negative persons. This has also been confirmed in many longitudinal as well as cross-sectional studies.

D Hansen et al[30,] Maugendre D et al[19] showed that the duration of diabetes doesn't influence development of AITD. The Indian study by Menon PS. [35] et al also observed that the thyroid autoimmunity did not change with duration.

In the report by Guillermo E. Umpierrez et al[6] most subjects with positive TPO antibodies (17 of 18) tested positive at the beginning of the study and remained positive throughout the study period. Only one patient

with an initial negative TPO titer developed low-TPO titer after 12 years of follow-up.

In the prospective study by Gemma C et al [4], TPOA was measured only at the onset of diabetes. Future conversion to positivity was not assessed. But only one of the initial TPOA negative individuals developed hypothyroidism who later turned out to be positive for antibody.

According to Olga Kordonouri et al[9] prevalence increases with increasing duration. O Kordonouri, R Hartmann et al[23] and Jennifer M. Barker et al[34] favour the same. Adriana Franzese et al [28] found a higher prevalence in those with longer duration particularly when they are in peripubertal age group.

Whether thyroid autoimmunity prevalence is higher in patients with longer duration of diabetes needs further clarification by longitudinal analysis.

CONCLUSIONS

- There is a high prevalence of thyroid autoimmunity in individuals with type 1 diabetes. A subset of patients develops thyroid dysfunction.

- Prevalence of thyroid autoimmunity as indicated by TPOA positivity is more than that seen among general population.

- Prevalence of hypothyroidism is more than that seen among general population. (last two interpretations are based on comparisons done using standard publications[15])

- Most of the patients develop subclinical form of the disease thus reducing the possibility of clinical suspicion.

- Gender, age and duration of diabetes may or may not have a significant association with autoimmune thyroid disease.

- In summary, our study confirms the association between autoimmune hypothyroidism and type 1 diabetes and suggests that all subjects with type 1 diabetes, particularly those with positive TPO antibodies, should undergo annual screening by serum TSH measurement to detect asymptomatic thyroid dysfunction.

SCOPE FOR FUTURE STUDIES

Organ-specific autoantibodies provide a simple way to screen for autoimmunity in the susceptible population and possibly prevent morbidity and mortality. However, the specific strategy for screening is an area of active debate and research . Long-term prospective studies are needed to identify the natural history of autoimmunity in patients with type 1 diabetes.

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PROFORMA

NAME :

SEX :

AGE :

DURATION OF DIABETES :

SYMPTOMS/SIGNS OF HYPOTHYROIDISM :

SYMPTOMS/SIGNS OF HYPERTHYROIDISM :

CO EXISTING MEDICAL ILLNESS :

THYROID PROFILE

TOTAL T3 :

TOTAL T4 :

TSH :

TPO ANTIBODY :

MASTER CHART

S.NO	Age	Sex	Diabetes duration	TPOA	T3	T4	TSH	Thyroid status
1	14	F	1	--	1.1	4.7	2.7	euthyroid
2	18	F	3	--	1.4	5.6	0.9	euthyroid
3	20	F	2	--	0.8	8.1	3.1	euthyroid
4	24	M	7	--	0.9	9	4.4	euthyroid
5	17	F	1	+	0.8	4.6	9.4	hypothyroid
6	23	M	5	--	1.1	7.1	2.8	euthyroid
7	15	F	4.5	--	0.8	5.4	3.7	euthyroid
8	22	M	3.5	--	1.4	4.6	1.4	euthyroid
9	21	F	0.5	+	1.2	7	1.8	euthyroid
10	18	M	2.5	--	0.8	10	4.8	euthyroid
11	27	F	4	+	0.9	5.2	7.2	hypothyroid
12	14	M	1	--	1.1	4.4	0.8	euthyroid
13	13	M	0.25	--	0.9	9.2	3.4	euthyroid
14	18	F	4	--	1.3	4.8	4.4	euthyroid
15	17	M	2	--	0.8	8.2	2.2	euthyroid
16	19	F	1.5	--	1.3	9.1	1.6	euthyroid
17	17	M	3	--	1.2	7.7	2.9	euthyroid
18	17	M	2.5	--	1.8	10.5	2.9	euthyroid
19	20	F	2.5	--	0.9	6.5	1.9	euthyroid
20	20	M	1	--	1.1	6.3	3.9	euthyroid
21	15	F	1.25	--	1.4	8.4	4.8	euthyroid
22	21	M	1.5	--	0.8	6.2	1	euthyroid
23	14	M	1	--	0.9	4.9	2.6	euthyroid
24	16	F	4	+	1	4.6	4.7	euthyroid
25	24	F	5	--	1.3	10	4.4	euthyroid
26	22	M	4	--	1.2	7.3	3.8	euthyroid
27	21	F	3	--	0.8	5.4	3	euthyroid
28	18	M	2	--	1.1	4.3	2.8	euthyroid
29	14	F	0.25	+	1	5.2	4.1	euthyroid
30	20	F	3	--	0.8	6.6	3	euthyroid
31	15	F	1	--	1.1	8.6	3.4	euthyroid
32	18	M	2	+	0.8	5.4	9.8	hypothyroid
33	20	M	3	--	1.2	5.9	1.9	euthyroid

34	23	M	5	--	1.1	6.7	1	euthyroid
35	32	F	4	--	0.9	10.2	4.5	euthyroid
36	29	M	5	--	1.2	7.6	2.7	euthyroid
37	26	M	6	+	0.8	7.2	4	euthyroid
38	14	F	1.5	--	1	9.4	3.2	euthyroid
39	15	F	2	--	1.1	8.8	2.6	euthyroid
40	19	F	4	+	0.9	5.1	9	hypothyroid
41	21	M	2	--	1.3	4.2	3.8	euthyroid
42	13	M	0.5	--	1.2	10	2.8	euthyroid
43	32	F	9	--	1.1	6.7	4.4	euthyroid
44	30	M	9	+	1	4.8	3.8	euthyroid
45	14	M	4	--	1.2	4.5	4.1	euthyroid
46	20	F	5	--	0.8	5.4	2.4	euthyroid
47	31	M	6	--	1.3	7.8	3.6	euthyroid
48	29	F	6	--	1.4	6.1	3.9	euthyroid
49	26	F	12	+	0.4	3	36.2	hypothyroid
50	25	M	4	--	1.1	9.2	3.2	euthyroid
51	15	F	5	--	1	8.6	4.2	euthyroid
52	13	M	0.5	--	1.2	8.2	4.1	euthyroid
53	18	F	2.5	--	0.9	8.6	1.8	euthyroid
54	19	F	1	--	1.3	5.5	3.8	euthyroid
55	14	F	3.5	+	0.8	6.1	8	hypothyroid
56	18	M	2	--	1.2	8.1	2.5	euthyroid
57	20	F	2	--	1	4.9	9.4	hypothyroid
58	27	M	3	--	1.1	10.2	4.2	euthyroid
59	26	M	7	+	1	6.8	10	hypothyroid
60	21	F	4.5	--	1.4	9.9	0.9	euthyroid
61	18	F	4	--	0.9	11	1.8	euthyroid
62	22	M	4	--	1.2	5.4	3.8	euthyroid
63	21	M	1	--	1.1	6.4	3.7	euthyroid
64	30	F	7	--	0.9	4.6	4.4	euthyroid

ABBREVIATIONS

T1D	:	TYPE 1 DIABETES MELLITUS
AITD	:	AUTOIMMUNE THYROID DISEASE
TPOA	:	THYROID PEROXIDASE ANTIBODY
T3	:	TRI-IODOTHYRONINE
T4	:	THYROXINE
TSH	:	THYROID STIMULATING HORMONE
TRH	:	THYROTROPIN RELEASING HORMONE
TG AB	:	THYROGLOBULIN ANTIBODY
CD	:	COELIAC DISEASE
AD	:	ADDISONS DISEASE
HLA	:	HUMAN LEUKOCYTE ANTIGEN
APS	:	AUTOIMMUNE POLYENDOCRINE SYNDROME

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YEAR: 2005-2008

INSTITUTION: INSTITUTE OF INTERNAL MEDICINE,
MADRAS MEDICAL COLLEGE,
GOVERNMENT GENERAL HOSPITAL,
CHENNAI.

DISSERTATION TITLE: “ THYROID DISORDERS IN TYPE 1 DIABETES MELLITUS.”